requests that they be withdrawn.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 134, 135, 137-142 and 144-146 under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. Specifically, the Examiner alleges that, although the claimed methods are enabled for using the NADE protein of SEQ ID NO:13, these methods are not enabled for proteins of SEQ ID NOs:30-39 because applicant has not shown that these proteins are NADE proteins. The Examiner further alleges that homology alone is insufficient to demonstrate that the proteins of SEQ ID NOs:30-39 are NADE proteins and that applicant has not provided guidance or working examples of the function of these proteins.

In response, applicant respectfully traverses the Examiner's rejection.

Claims 134, 135, 137-142 and 144-146 provide methods of identifying agents capable of regulating apoptosis, using NADE proteins. Applicant maintains that, in light of the disclosure, one skilled in the art would be able to predict which proteins can bind to p75 and regulate apoptosis, both features of NADE proteins. The specification discloses *inter alia* at page 55, lines 11-14 that "mapping studies revealed that NADE protein interacts with the cell death domain (amino acid residues 338-393) which is identical among mouse, rat and human." Further, the Examiner conceded on page 3, paragraph A, of the April 23, 2003 Office Action, that applicant has shown that NADE interacts with the *cell death domain* of p75,

and has shown that apoptosis *only* occurs when p75 and NADE are expressed together. In addition, Mukai, Jun et al. ("NADE, A $p75^{NTR}$-Associated Cell Death Executor, Is Involved In Signal Transduction Mediated BY The Common Neurotrophin Receptor $p75^{NTR}$", J. Bio. Chem. (2000) 275(23):17566-17570, submitted as Exhibit E with the March 8, 2001 Supplemental Information Disclosure Statement) discloses on page 17569, paragraph 2 and Figure 2B, that the "C-terminal portion of NADE (amino acid residues 81-106) is necessary for the interaction with $p75^{NTR}$" cell death domain. These features functionally describe the NADE proteins. Further, as the Examiner concedes, the specification discloses structural features of NADE proteins, namely hydrophilic and acidic properties and, in addition to its binding site for p75, two significant motifs: the leucine-rich nuclear export signal (NES) and ubiquitination sequences. These functional and structural features together provide an adequate description of the NADE proteins which would enable one skilled in the art to recognize, without undue experimentation, which proteins are NADE proteins. In addition, the specification contrasts other proteins that may bind to p75 but do not regulate apoptosis, e.g. TRAF6 which binds to the extracellular domain of p75. Accordingly, applicant maintains that one skilled in the art would be able to predict, without undue experimentation, which proteins would be able to bind to the cell death domain of p75 to regulate apoptosis, i.e. which proteins are NADE proteins.

The Examiner further states that Figure 1H of the specification only discloses the homology among mouse, rat and human NADE proteins, SEQ ID NOs:30-39, and that without any working examples of the function of these sequences, the

claimed methods are not enabled for proteins of SEQ ID NOs:30-39.

Applicant respectfully disagrees with the Examiner's statement. According to M.P.E.P. §2164.02, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." Further, "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art and information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner." Applicant maintains that the Examiner has not set forth such adequate reasons. Nevertheless, Figure 1H discloses homologous mouse, rat and human NADE proteins which exhibit all structural and functional features of NADE proteins. Applicant maintains that the homology of these NADE sequences, as shown in Figure 1H, in combination with the above-mentioned disclosure in the specification and teaching of Mukai, Jun et al., provides adequate disclosure for one skilled in the art to distinguish NADE proteins that, when bound to p75, regulate apoptosis, from other p75-binding proteins that do not regulate apoptosis.

The Examiner further rejects claims 134, 135, 137-142 and 144-146 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that is not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor, at the time the application was filed, was in possession of the claimed invention. Specifically, the Examiner again asserts that although the specification adequately describes methods using NADE proteins of SEQ ID NO:13, applicant has not shown that the proteins of SEQ ID NOs:30-39 are in fact NADE proteins.

In response, applicant respectfully traverses the Examiner's rejection.

Applicant contends that the NADE genus was disclosed in the specification as filed, adequately describing the NADE-specific structural and functional features and providing numerous embodiments of its species. As stated above, NADE proteins are hydrophilic and acidic and possess, in addition to their binding site for the p75 neurotrophin receptor cell death domain (SEQ ID NO:1), two significant motifs: the leucine-rich nuclear export signal (NES) and ubiquitination sequences. NADE proteins bind to the cell death domain of p75, specifically to the amino acid residues 338-393, with the C-terminus of NADE being a necessary component of the interaction. In addition, the specification discloses various species of human, mouse and rat NADE, as set forth in SEQ ID NOs:12-13 and SEQ ID NOs:30-39, which illustrate these specific features. Accordingly, applicant maintains that the disclosure as filed provides sufficient description of the NADE genus and its role in the regulation of $p75^{NTR}$-mediated apoptosis.

The Examiner objects to the specification under 35 U.S.C. §112, first paragraph, as allegedly containing new matter.

The Examiner requests a statement in accordance with 37 C.F.R. §1.821(f).

Applicant notes that this objection has been addressed by the submission of a substitute sequence listing, in both paper and computer-readable forms, accompanied by a Statement In Accordance With 37 C.F.R. §1.821(f), as Exhibit C, in a November 27, 2002 Amendment In Response To November 1, 2002 Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant attaches hereto, as **Exhibit A**, a copy of the Statement In Accordance With 37 C.F.R. §1.821(f) filed with the November 27, 2002 Amendment. Accordingly, applicant maintains that the sequence listing and statement as filed in the November 27, 2002 Amendment satisfies the requirements of 37 C.F.R. §1.821-1.825.

In view of the above remarks, applicant maintains that claims 134, 135, 137-142 and 144-146 and the specification satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C §112, Second Paragraph

The Examiner rejected claims 134, 135, 137-142 and 144-146 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that the metes and bounds of the NADE protein genus are not specific to NADE proteins.

In response, applicant respectfully traverses the Examiner's rejection.

In support of the rejection, the Examiner states that the most specific characteristic of the NADE genus is that these proteins possess a p75 binding site.

Applicant respectfully disagrees with the Examiner's assertion. Applicant contends that the language in claims 134, 135, 137-142 and 144-146 particularly points out and distinctly claims the subject invention. Applicant maintains that, contrary to the Examiner's statement, the specification does not merely disclose that NADE proteins contain a p75 binding site, but clearly and specifically details the NADE p75 binding site. As stated above, the specification discloses that NADE proteins bind to the p75 neurotrophin receptor *at its cell death domain (SEQ ID NO:1), amino acid residues 338-393*, possess two other significant motifs, namely NES and ubiquitination sequences and that the C-terminus of NADE plays an essential role in the binding of the cell death domain of p75. Accordingly, applicant maintains that claims 134, 135, 137-142 and 144-146 particularly point out and distinctly claim methods for identifying apoptosis modulators using NADE proteins, as the specification clearly defines the NADE protein genus.

In view of these remarks, applicant maintains that claims 134, 135, 137-142 and 144-146 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Summary

For the reasons set forth hereinabove, applicant respectfully requests that the Examiner reconsider and withdraw the rejections, and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

1/9/07
Date

Alan J. Morrison
Reg. No. 37,399